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The Difficulty of using a Biological Marker for Alcohol Use: A Recent Historical Overview

David Adler

According to the National Health Interview Survey from 2011, 52% of adults over the age of 18 in the United States are regular drinkers [1]. However, because of the difficulty of defining alcoholism scientifically, there are few widespread statistics regarding the proportion of this group who are problem drinkers. This brings us to the field of science. Scientists have wanted to set a biological marker on alcoholism to track alcohol use and determine what separates a regular drinker from an alcoholic. A biological marker could increase the effective surveillance of rehabilitation, gather data from patients more effectively, help in overcoming patient denial and treat alcoholism scientifically and objectively. However, while some tests have shown more consistency than others, there still does not exist an ideal biological marker for alcoholism and related treatment. The complexity of chemicals involved and patient genetic predisposition make this pursuit even more complex. In this paper I will discuss the more prominent and significant biological markers used in the past and present to detect alcohol use, explain their association to alcohol consumption and their functionality in the field.

Trait Markers

Biological markers indicate the progress or state of a condition by gathering information about biochemical substances within the body. Trait markers reveal a subject's inherited risk towards alcohol consumption (i.e. family genetics) [2]. A useful trait marker molecule must satisfy three criteria: Passed down by genes, associated with the disease in question and should be independent of the subject's disease status as explained by Ratsma et al [3]. State markers, on the other hand, are measures revealing the short-term of substance intake of the patient while trait markers reveal genetic inheritance of the patient. Ideally, a good biological marking test would require the combination of the two markers.

The early research of trait markers began with a focus on familial alcohol use divided into a subject's history of positive or negative familial alcoholism (FHP & FHN respectively) [4]. This knowledge was used in combination with ethanol sensitivity testing and Monoamino Oxidase activity but many inconsistencies in methodology over different tests and conflicting results created unnecessary speculation and lowered interest for further research. For example some studies showed that FHP subjects were less sensitive to small effects of alcohol than FHN subjects [5] [6]. However, other studies found opposite data or even neutral findings [7] [8].

Results from Tabakoff et al [9] depicted lower platelet *adenylate cyclase* (AC) activity in alcoholics, however, Devor et al [10] replicated the study with no significant link. Recently researchers observed the same pattern as Tabakoff et al but noticed that other drug consumption affected AC activity [11] making AC an unsuitable measure without further research. There has also been an observed link between people who are

alcohol dependent and have lower levels of the neurotransmitter, *gamma-aminobutyric acid* (GABA), than do non-alcohol-dependent people [3]. But because it is not independent of the status of the disease it therefore doesn't match the criteria of a good trait marker. Dopamine reception in the 1990s was found to have an A1 allele associated with severe form of alcoholism [12] and as some research suggests there is lower level of dopamine receptor activity with alcoholic men [3]. However, this conflicts with findings from Balldin et al [13] that demonstrated that alcoholics showed an elevated response to dopamine after a short withdrawal period, making dopamine an unlikely trait marker candidate.

As of now, the measurement of serotonin and beta-endorphins shows the greatest potential for clinical widespread use. The neurotransmitter beta-endorphin functions as an opioid to produce natural pain relief. Studies have found that alcoholics have lower levels of beta-endorphin than non-alcoholics [14], however, because it is not independent of the status of the disease for the person, it does not fit the criteria. Research has shown lower levels of the amino acid tryptophan, which produces the neurotransmitter serotonin, with those who consume excessive alcohol [3]. Research into serotonin transportation has shown higher serotonin transporter activity with alcoholics and with children of alcoholics than non-alcoholics [15], thus fitting the criteria of a good trait marker. While many trait markers for alcoholism exist, few of them meet the necessary criteria but there is some promise in further research into serotonin and beta-endorphins.

State Markers

Our discussion then moves to that of state markers. The most common and important state marker is the testing of ethanol levels in the bloodstream most commonly tested with a Breathalyzer for a subject's Blood Alcohol Content (BAC) or through urine screening. However, the body quickly detoxifies ethanol and urine screening is unable to both represent chronic/long term and recent drinking. Thus, ethanol is only useful for short-term use indication and is used for mostly police and professional settings and screenings [17].

Clinicians currently measure the activity of liver enzymes and red blood cell volume. One measure they use is that of the liver enzyme *gamma-glutamyltransferase* (GGT). This glycoprotein aids in digestion and is involved in bile production. Elevated GGT levels can be an early indicator of liver disease but it is not that sensitive to alcohol consumption and is only useful with consumption of heavy drinkers. GGT levels are also affected by digestive disease [2]. Another widespread measure was that of the mean corpuscular volume (MCV) of red blood cells. This measure shows an alcoholic's MCV stays high regardless of abstinence but since other conditions affect MC, it is not an ideal state marker [18]. In addition, research in the 1990s indicated that the use of other drugs affected MCV and GGT levels [19].

Still used today are both the enzymes *aspartate Aminotransferase* (AST) and *alanine aminotransferase* (ALT), however, they represent more an indication of liver disease than for alcohol use. Research from the 1990s has shown that when healthy individuals binge drink their AST and ALT levels in the blood increase [20]. However, AST is found in other internal organs including the kidney and brain. Thus, these

enzymes are more to confirm knowledge of liver damage than used as a state marker and they are less sensitive with subjects under 30 and over 70 [1] [4]. These enzymes have not been furthered researched as of today.

A very well characterized indicator is that of the *Carbohydrate-Deficient Transferrin* (CDT) that is involved in the transport and delivery of iron in the body and shown [21] to have higher levels in alcoholics. CDT is a good indicator in evaluating alcoholism treatment because of its half-life of 14 days [22]. However, the successful findings of CDT in the past does not match up to our present concerns that show it is too specific of a measure and is too inclined to give false negative readings. However, recent improvements have developed agents that can specifically detect CDT [23] and it has increased success when paired it with GGT tests [24]. CDT remains a good indicator of heavy alcohol consumption.

Some of the newer state biological markers include *Plasma Sialic Acid Index of apolipoprotein J* (SIJ) and the compound *acetaldehyde* show potential. SIJ transports lipids into the blood and has shown that sialic acid particles decrease after alcoholic consumption. It is more specific than CDT because it has four times the acid chains as CDT thus it shows promise for further testing [25]. Tests using high-performance liquid chromatography, known as whole blood-associated *acetaldehyde* assay (WBAA), have given very specific and sensitive results [21] but with FDA approval pending it still requires more legitimization and credibility despite its amazing potential.

The difficulty with choosing an effective state marker includes the effect of other drugs, gastro-intestinal diseases involved and differing subject usage levels over time that can affect the activity of relevant enzymes. So unfortunately no state marker exists that is durable against each of these informal criteria but research in SIJ, *acetaldehyde* and CDT paired with GGT show good potential in the field.

In conclusion, there is no single test to accurately represent the long term and short-term consumption of alcohol. The best device is to use a combination of consistent state and trait marker tests in supplement with a questionnaire. A questionnaire poses threats to internal validity through the subject's poor memory recall and deliberate falsification of data but it consistently serves as standard measure of alcohol consumption. There are also many more possible biological markers of alcohol use that I have not listed but each fraught with their own unique set of problems. Similar to the position of scientists in the 1990s, there is much more research needed in order to exact a better combination of measures to develop an equally specific and sensitive marker. Biomarkers will help to objectify definitions of alcohol abuse that the DSM-IV can only do with subjective description. Thus research into these biological markers will not only develop testing that will help to understand the risk of genetic factors but also aid in the treatment of alcoholics through a greater understanding of alcohol use/abuse and a more efficient surveillance of recovery.

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